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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/717,984	NEWMAN, WALTER	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 23-42 are pending.

2. Upon reconsideration the Examiner has extend the search to cover SEQ ID NO: 5 and 23 and the condition of sepsis.

3. Applicant's election of Group IV, claims 23-34 (now 23-42) drawn to a method of treating a condition in a patient characterized by activation of an inflammatory cytokine cascade comprising administering to a composition comprising an antibody that binds to HMGB polypeptide or a biological active fragment thereof and an agent, wherein the antibody binds to SEQ ID NO: 1 species and the condition is rheumatoid arthritis species, filed on 1/25/06, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

4. Claims 23-42 are under consideration in the instant application as they read on a method of treating a condition in a patient characterized by activation of an inflammatory cytokine cascade comprising administering to a composition comprising an antibody that binds to HMGB polypeptide or a biological active fragment thereof and an agent, wherein the antibody binds to SEQ ID NO: 1, 5 and 23 species and the condition is rheumatoid arthritis and sepsis as the species.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 23-42 arerejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 23 contains the trademark/trade name etanercept. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See Ex parte Simpson, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to describe a recombinant human soluble tumor necrosis factor-alpha (TNFα) receptor and, accordingly, the description is indefinite.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 37 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The phrase "human antibody" claimed in claims 37, represents a departure from the specification and the claims as originally filed.

Applicant's amendment filed 3/30/06 points to the specification page 30, lines 4-9 for support for the newly added limitation "human antibody" as claimed in claim 37. However, the specification does not provide a clear support for "human antibody". The Examiner notes that the specification on page 30, lines 4-9, is limited in the scope to only a human antibody obtained by phage display technology, while claim 37 is generic claims to any human antibodies including Human Polyclonal Antibody Production System and human antibody products derived from transgenic mouse technology. The instant claims now recite a limitation, which was not clearly disclosed in the specification and recited in the claims as originally filed.

9. Claims 23-26, 29, 32-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a method of treating a condition in a patient characterized by activation of an inflammatory cytokine cascade comprising administering to said patient a composition comprising an antibody that binds to HMGB1 polypeptide consisting of SEQ ID NO: 1, 5 or 23 and an agent that inhibts TNF biological activity, wherein said agent is selected from the group consisting of infliximab, etanercept, adalimumab, CDP870, CP571, Lenercept and Thalidomide.

Applicant is not in possession of a method of treating a condition in a patient characterized by activation of an inflammatory cytokine cascade comprising administering to said patient a composition comprising an antibody that binds to any HMGB polypeptide or a biological active fragment thereof and an agent that inhibts TNF biological activity, wherein said agent is selected from the group consisting of infliximab, etanercept, adalimumab, CDP870, CP571, Lenercept and Thalidomide in claim 23, wherein the HMGB polypeptide a any mammalian HMGB polypeptide, in claim 25, wherein the HMGB polypeptide is any HMGB1 polypeptide in claim 26.

Applicant has disclosed only amino acid of SEQ ID NO: 1, 5 and 23; therefore, the skilled artisan cannot envision all the contemplated HMGB sequence possibilities recited in the instant claims. Further, HMGB1 indicates that there are other HMGBs such as HMGB2, 3... . Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

11. Claims 23-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Pat. No. 6,468,533 in view U.S. Pat. No. 6,677,321.

The `533 patent teaches a method of treating rheumatoid arthritis and sepsis which are characterized by activation of an inflammatory cytokine cascade comprising administering to a patient a composition comprising an antibody that binds to an HMGB polypeptide or a biologically active fragment thereof (see col. 3, lines 4-18, and col. 4, lines 4-6 and patented claims 1-6 in particular) and an agent such as TNF (see col., 5, line 16, or an antibody to TNF

(see col., 5, line 16-17 in particular), wherein the composition further comprises a pharmaceutically acceptable carrier (see col., 7, line 64 col., 8, line 2 in particular). The `533 patent further teaches that it has become apparent that a large, highly diverse group of proteins including several transcription factors and other DNA-interacting proteins, contain one or more regions similar to HMG1, and this feature has come to be known as the HMG1 box or HMG1 domain (see col., 2, lines 9-14 in particular).

The `533 patent teaches monoclonal, humanized, and human antibodies against native or recombinant HMG1 or fragments thereof (see col. 9, lines 23-42 in particular). Further, the `533 patent teaches a pharmaceutical composition comprising an antagonist or inhibitor of HMG1, wherein the antagonist is antibodies that bind to an HMG1 protein, to treat conditions mediated by the inflammatory cytokine cascade (see col. 5, lines 3-6 in particular). The `533 patent further teaches neutralizing antibodies against HMG1 (i.e., those that inhibit biological activities of HMG1 particularly with regard to its pro-inflammatory cytokine-like role) are preferred for therapeutic applications. Examples of such useful antibodies include but are not limited to polyclonal, monoclonal, chimeric, single-chain, and various human or humanized types of antibodies, as well as various fragments thereof such as Fab fragments and fragments produced from specialized expression systems (see col., 9, under HMG1-directed antibodies and Example 4 in particular). The `533 patent teaches a composition comprising an antibody that specifically binds an HMG1 protein, wherein the antibody inhibits HMG1-mediated activation of the inflammatory cytokine cascade caused inflammation such as sepsis (see patented claims 1-6 in particular). The `533 patent teaches that treatment with anti-HMG1 antibodies provided full protection from LD_{100} doses of LPS in mice (vertebrate). HMG1 is inducible by TNF and IL-α, and dose-dependently stimulates TNF release from huPBMCs. TNF is a marker of macrophage activation (see col., 7, lines 25-55, in particular). Finally, the `533 patent teaches that TNF stimulates the release of HMG1 from murine macrophage RAW 264.7 cells (see table 1 in particular). Therefore, antibodies to HMG1 that neutralize or antagonize the biological activity of HMG1would inhibit the release of TNF from the macrophage cells.

While the prior art teachings may be silent as to the specific sequence for SEQ ID NO:1, 5 and 23 recited in the claims, per se; however, the referenced anti-HMG1 antibodies has the same recited functional property. For example, the anti-HMG1 antibodies neutralize or antagonize the biological activity of HMG1 (see col. 13, lines 1-3) particularly with regard to its pro-inflammatory cytokine-like role (see col. 9, lines 32-34 in particular), wherein the HMG1-mediated activation of the inflammatory cytokine cascade causes inflammation (see patented claim 4 in particular); the antibody in the reference is the same as the antibody in the claimed method.

The claimed invention differs from the reference teachings only by the recitation that the agent is infliximab or etanercept in claim 23.

The `321 patent teaches that treatment with a chimeric mAb to TNF-α has been shown to suppress inflammation and improve patient well-being in rheumatoid arthritis (RA). Examples of

TNF antagonists shown to be effective for short term treatment include infliximab and etanercept (see col.5, line 66 to col., 6, line 3 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the TNF or anti-TNF antibody taught by the `533 patent with the infliximab or etanercept taught by the `321 patent in a method of treating a condition in a patient characterized by activation of an inflammatory cytokine cascade.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such TNF inhibitors shown to be effective for short term treatment of inflammation such as RA as taught by the `321.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

12. Claims 23-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. 20030060410 publication in view U.S. Pat. No. 6,677,321.

The `410 publication teaches and claims a method of treating a condition in a patient characterized by activation of an inflammatory cytokine cascade, comprising administering to the patient a purified preparation of antibodies that specifically bind to a vertebrate high mobility group protein (HMG)B box but doe not specifically bind to non-B-box epitopes of HMG, in an amount sufficient to inhibit the inflammatory cytokine cascade (see published claim 14 in particular). The `410 publication teaches that the composition can inhibit a condition characterized by activation of an inflammatory cytokine cascade. The composition can further comprise an antagonist or an early sepsis mediator. The antagonist on an early sepsis mediator is preferably an antagonist of a cytokine such as TNF, more preferably an antibody to TNF receptor antagonist (see 12¶ in particular), wherein the condition is sepsis or rheumatoid arthritis (see 13¶ in particular). Further, the `410 publication teaches that the antibodies can inhibit a biological activity of an HMG B box polypeptide, for example, the release of a proinflammatory cytokine from a vertebrate cell treated with HMG, In preferred embodiments, the HMG B box is a mammalian HMG B box, for example, a human HMG B box, more preferably an HMG1 B box, most preferably the HMG1 B box with the amino acid sequence of claimed and published SEQ ID NO:5 or SEQ ID NO:20. In another embodiment, the antibodies bind a specific polypeptide sequence of the HMG1 B box, comprising amino acids 1-20 of SEQ ID NO:20 (SEQ ID NO: 16), or comprising amino acids 1-20 of SEQ ID NO:5 (claimed and published SEQ ID NO:23), or consisting of amino acids 1-20 of SEQ ID NO:20 (SEQ ID NO: 16), or consisting of amino acids 1-20 of SEQ ID NO:5 (SEQ ID NO:23). The vertebrate cell is also preferably a mammalian macrophage. In some embodiments, the antibodies are preferably humanized (see 14¶ in particular). The `410 publication also teaches that "antibodies" as used herein includes

monoclonal and polyclonal antibodies, chimeric, single chain, simianized antibodies and humanized antibodies, as well as Fab fragments, including the products of an Fab immunoglobulin expression library (see 112¶ in particular). In addition, the `410 publication teaches phage display technology can also be utilized to select antibody genes with binding activities towards the polypeptide either from repertoires of PCR amplified v-genes of lymphocytes from humans screened for possessing anti-B box antibodies or from naive libraries (see 118¶ in particular).

Claims 27 and 28 are included because an antibody to SEQ ID NOS: 5 and 23 would bind to claimed SEQ ID NO:1 because SEQ ID NOs: 5 and 23 are fragments of SEQ ID NO: 1 and an antibody to the fragments would bind the larger sequence.

The claimed invention differs from the reference teachings only by the recitation that the agent is infliximab or etanercept in claim 23.

The `321 patent teaches that treatment with a chimeric mAb to TNF-α has been shown to suppress inflammation and improve patient well-being in rheumatoid arthritis (RA). Examples of TNF antagonists shown to be effective for short term treatment include infliximab and etanercept (see col.5, line 66 to col., 6, line 3 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the TNF or anti-TNF antibody taught by the `410 publication with the infliximab or etanercept taught by the `321 patent in a method of treating a condition in a patient characterized by activation of an inflammatory cytokine cascade.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such TNF inhibitors shown to be effective for short term treatment of inflammation such as RA as taught by the `321.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

13. Claims 23-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Pat. 6,448,223 in view of U.S. Pat. No. 6,677,321.

The `223 patent claims a method for treating a condition characterized by activation of the inflammatory cytokine cascade, comprising administering an effective amount of an antibody that specifically binds an HMG1 protein, wherein said antibody inhibits HMG1-mediated activation of the inflammatory cytokine cascade (see patented claim 1), wherein the method further comprising administering a second agent in combination with the antibody that specifically binds an HMG1 protein, wherein the second agent is an antagonist of an early sepsis

mediator (see patented claim 2), wherein the second agent is an antagonist of a cytokine selected from the group consisting of TNF, IL-1.alpha., IL-1.beta., MIF and IL-6 (see patented claim 3), wherein the second agent is an antibody to TNF or an IL-1 receptor antagonist (IL-1ra) (see patented claim 4). Further the `223 patent teaches a method for treating sepsis, comprising administering an effective amount of an antibody that specifically binds an HMG1 protein and inhibits HMG1-mediated activation of the inflammatory cytokine cascade (see patented claim 5), the method further comprising administering a second agent in combination with the antibody that specifically binds an HMG1 protein, wherein the second agent is an antagonist of an early sepsis mediator, wherein the early sepsis mediator is selected from the group consisting of TNF, EL-1.alpha., IL-1.beta., MIF and IL-6 (see patented claim 6 in particular), wherein the second agent is an antibody to TNF or MIF, or is an IL-1 receptor antagonist (IL-1ra) (see patented claim 7 in particular). The `223 patent further teaches that diseases and conditions mediated by the inflammatory cytokine cascade are numerous such as rheumatoid arthritis (see co., 4, line 16 in particular). The `223 patent further teaches that the neutralizing antibodies against HMG1 (i.e., those that inhibit biological activities of HMG1 particularly with regard to its pro-inflammatory cytokine-like role) are preferred for therapeutic applications. Examples of such useful antibodies include but are not limited to polyclonal, monoclonal, chimeric, single-chain, and various human or humanized types of antibodies, as well as various fragments thereof such as Fab fragments and fragments produced from specialized expression systems (see col. 9, lines 45-63 in particular).

Claims 30-31 are included because the referenced polyclonal antibodies against HMG1 of claimed SEQ ID NO: 1 would bind the fragments of SEQ ID NO: 5 and 23 (see example 4).

The claimed invention differs from the reference teachings only by the recitation that the agent is infliximab or etanercept in claim 23.

The `321 patent teaches that treatment with a chimeric mAb to TNF-α has been shown to suppress inflammation and improve patient well-being in rheumatoid arthritis (RA). Examples of TNF antagonists shown to be effective for short term treatment include infliximab and etanercept (see col.5, line 66 to col., 6, line 3 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the TNF or anti-TNF antibody taught by the `223 patent with the infliximab or etanercept taught by the `321 patent in a method of treating a condition in a patient characterized by activation of an inflammatory cytokine cascade.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such TNF inhibitors shown to be effective for short term treatment of inflammation such as RA as taught by the `321.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at

the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. Claims 23-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al in view of U.S. Pat. 6,448,223 and U.S. Pat. No. 6,677,321.

Wang et al teach that HMG-1 is a late mediator of endotoxin lethality in mice, an animal model of human sepsis. Wang et al teach that endotoxin stimulates macrophages to release large quantities of tumor necrosis factor (TNF) and IL-1, which can precipitate tissue injury and lethal shock (endotoxemia). Delayed administration of antibodies to HMG-1 attenuated endotoxin lethality in mice, and administration of HMG-1 itself was lethal. Septic patients who succumbed to infection had increased serum HMG-1 levels, suggesting that this protein warrants investigation as a therapeutic target (see abstract). Wang et al teach that recombinant rat HMG-1 (claimed SEQ ID NO: 1) was used to generate polyclonal antibodies (see page 249, 1st col., 1st full paragraph in particular). Further, administration of anti-HMG-1 in two doses (one 30 min before LPS and one 12 hours after LPS) increased the survival rate of the mice to 30%. With three doses of antiserum (−30 min, +12 hours, +36 hours), 70% of the treated mice survived, as compared with 0% survival in controls treated with three matched doses of preimmune serum ($P < 0.05$). No late death occurred over 2 weeks, indicating that anti-HMG-1 did not merely delay the onset of LPS lethality, but provided lasting protection (see page 249, 3rd col., 1st paragraph in particular). Furthermore, Wang et al teach that macrophages release HMG-1 when exposed to the early, acute cytokines, indicating that HMG-1 is also positioned as a mediator of other inflammatory conditions associated with increased levels of TNF and IL-1 (for example, rheumatoid arthritis and inflammatory bowel disease). Wang et al conclude that the observations that HMG-1 itself is toxic, and that anti-HMG-1 prevents LPS lethality, point to HMG-1 as a potential target for therapeutic intervention (see page 251, last paragraph in particular).

Claims 30-31 are included because the referenced polyclonal antibodies would bind the fragments of SEQ ID NO: 5 and 23.

The claimed invention differs from the reference teachings only by the recitation that the agent is infliximab or etanercept in claim 23 and the antibodies recited in claims 37-42.

The teachings of the `223 patent have been discussed, supra.

The `321 patent teaches that treatment with a chimeric mAb to TNF-α has been shown to suppress inflammation and improve patient well-being in rheumatoid arthritis (RA). Examples of TNF antagonists shown to be effective for short term treatment include infliximab and etanercept (see col.5, line 66 to col., 6, line 3 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the infliximab or etanercept taught by the `321 patent with the anti-HMG1 antibody taught by the Wang in a method of treating a condition in a patient characterized by activation of

an inflammatory cytokine cascade and further to use a human, humanized, chimeric, single chain, or fab fragment antibody taught by the `223 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such TNF inhibitors shown to be effective for short term treatment of inflammation such as RA as taught by the `321. One skill in the art would have been motivated to use they a human, humanized, chimeric, single chain, or fab fragment antibody because they have low immunogenicity in human.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. No claim is allowed.

16. References V, W and X are cited on PTO FORM 892 to indicate the state of the art.

Abraham *et al.* HMG-1 as a mediator of acute lung inflammation. J Immunol. 2000 Sep 15;165(6):2950-4.

Yang *et al.* HMG-1 rediscovered as a cytokine. Shock. 2001 Apr;15(4):247-53.

Andersson et al High mobility group 1 protein (HMG-1) stimulates proinflammatory cytokine synthesis in human monocytes. J Exp Med. 2000 Aug 21;192(4):565-70

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

April 10, 2006

Maher Haddad

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